

Sub
C24
1. 45. (New) A composition of a stable, sterile, and injectable aqueous dispersion of a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm consisting essentially of

- (a) between about 1% to about 15% of propofol;
(b) between about 1% to about 8% of a propofol soluble diluent;
(c) between about 0.5% to about 5% of a surface-stabilizing amphiphilic agent;
and (d) a pharmaceutically acceptable water-soluble polyhydroxy additive that acts as a tonicity modifier;
- R2
(e) provided the ratio of propofol to diluent is about 1:4 to about 1:0.1 and the ratio of propofol to amphiphilic agent is about 1:0.8 to about 1:2.5, and the composition has a viscosity of from about 0.8 to about 15 centipoise, wherein the composition prevents microbial growth, defined as no more than 0.5 log increase from the initial inoculum, of each of *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus niger* for at least 7 days as measured by a test wherein a washed suspension of each said organism is added to a separate aliquot of said composition at approximately 1000 colony forming units per mL, at a temperature in the range 20-25°C, whereafter said aliquots are incubated at 20-25°C and are tested for viability of the microorganisms in the inoculated composition as determined by counting the colonies of said organism after 24, 48 hours and 7 days; and results in no irritation at the site of injection as evidenced by a test wherein said

composition is administered as a single daily bolus injection of 12.5 mg/kg, given on the

basis of body weight, for 2 successive days over a period of approximately 30 seconds, in the caudal vein of a rat such that no visual increase in the diameter of the rat tail is noted after 48 hours post injection.

46. (New) The composition of claim 45, wherein the surface stabilizing amphiphilic agent is a surface modifier selected from the group consisting of ionizable phospholipid, non-ionizable phospholipid, a mixture of ionizable phospholipid and cholesterol, a mixture of non-ionizable phospholipid and cholesterol, and mixtures thereof.

47. (New) The composition of claim 45, wherein the propofol-soluble diluent is selected from the group consisting of a synthetic fatty acid triglyceride, a natural fatty acid triglyceride, and mixtures thereof.

48. (New) The composition of claim 45, wherein the ratio of propofol to the amount of propofol-soluble diluent is from about 1:3 to about 1:0.5.

49. (New) The composition of claim 45, wherein the ratio of propofol to the amount of propofol-soluble diluent is from about 1:2 to about 1:1.

50. (New) The composition of claim 45, wherein the propofol-soluble diluent is a mixture of medium-chain triglyceride and vegetable oil.

51. (New) The composition of claim 50, wherein the ratio of medium-chain triglyceride to vegetable oil is from 1:3 to 3:1.

52. (New) The composition of claim 45, wherein the composition contains about 2% to about 10% of propofol.

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53. (New) The composition of claim 43, wherein the pharmaceutically acceptable water-soluble polyhydroxy additive provides the propofol containing dispersion with an osmolality of about 250 to about 700 milliosmolal.

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54. (New) The composition of claim 53, wherein the osmolality is about 300 to about 500 milliosmolal.

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55. (New) The composition of claim 45, wherein the viscosity is from about 2 to about 5 centipoise.

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(cont.)
56. (New) An injectable, stable, sterile, and antimicrobial aqueous dispersion comprising a water-insoluble microdroplet matrix of mean diameter from about 50 nm to about 1000 nm capable of inhibiting the growth of microorganisms and consisting essentially of about 1% to about 15% of propofol, up to about 7% of a propofol-soluble diluent, and about 0.8% to about 4% of a surface stabilizing amphiphilic agent, the aqueous phase comprising a pharmaceutically acceptable water-soluble polyhydroxy tonicity modifier, the dispersion being devoid of additional bactericidal or bacteriostatic preservative agents and causing no irritation at the site of injection.

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57. (New) The dispersion of claim 56, where the propofol and diluent are present in a ratio of about 1:4 to about 1:0.1 of propofol to diluent.

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58. (New) The dispersion of claim 56 where the propofol and amphiphilic agent are present in a ratio of about 1:0.8 to about 1:2.5 of propofol to amphiphilic agent.

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59. (New) The dispersion of claim 56 that has a viscosity of from about 0.8 to about 15 centipoise.

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~~60.~~ (New) The dispersion of claim ¹²~~56~~, wherein the propofol-soluble diluent is selected from the group consisting of a pharmaceutically acceptable saturated fatty acid triglyceride, a pharmaceutically acceptable unsaturated fatty acid triglyceride, and mixtures thereof.

¹⁷
~~61.~~ (New) The dispersion of claim ¹²~~56~~, wherein the propofol-soluble diluent is selected from the group consisting of pharmaceutically acceptable esters of medium chain fatty acids, pharmaceutically acceptable esters of long chain fatty acids, pharmaceutically acceptable triglycerides of medium chain fatty acids, and mixtures thereof.

¹⁸
~~62.~~ (New) The dispersion of claim ¹²~~56~~, wherein the propofol-soluble diluent is selected from the group consisting of isopropyl myristate, cholesteryl oleate, ethyl oleate, squalene, squalane, alpha-tocopherol, and mixtures thereof.

¹⁹
~~63.~~ (New) The dispersion of claim ¹²~~56~~, wherein the propofol-soluble diluent is a mixture of medium-chain triglyceride and vegetable oil.

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~~64.~~ (New) The diluent of claim ¹⁹~~63~~, wherein the ratio of medium-chain triglyceride to vegetable oil is from 1:3 to 3:1.

²¹
~~65.~~ (New) The dispersion of claim ¹²~~56~~, wherein the water-insoluble matrix contains about 2% to about 10% of propofol.

²²
~~66.~~ (New) The dispersion of claim ¹²~~56~~, wherein the surface stabilizing amphiphilic agent is a surface modifier selected from the group consisting of ionizable phospholipid, non-ionizable phospholipid, a mixture of ionizable phospholipid and cholesterol, a mixture of non-ionizable phospholipid and cholesterol, and mixtures thereof.

²³
67. (New) The dispersion of claim ¹²56, wherein the surface stabilizing amphiphilic agent is selected from the group consisting of charged phospholipid of natural sources, uncharged phospholipid of natural sources, hydrogenated lecithin, a synthetic phospholipid, a poloxamer, a poloxamine, a polyoxyethylene sorbitan ester, and mixtures thereof.

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68. (New) The dispersion of claim ¹²56, wherein the surface stabilizing amphiphilic agent is a combination of cholesterol and one or more charged or uncharged phospholipid of natural sources, hydrogenated lecithin, or synthetic phospholipids.

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69. (New) The dispersion of claim ¹²56, wherein the surface stabilizing amphiphilic agent is selected from the group consisting of 1,2-dimristoyl-sn-glycero-3-phosphocholine, 1,2-dimristoyl-sn-glycero-3-, egg lecithin, egg phosphatidylcholine, soy phosphatidylcholine, saturated soy phosphatidylcholine, soy lecithin, dimyristoylphosphatidylcholine, and dimyristoylphosphatidylglycerol.

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70. (New) The dispersion of claim ¹²56 that elicits an anesthetic effect in warm-blooded animal and human subjects upon intravenous administration.

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71. (New) The dispersion of claim ¹²56, wherein the tonicity modifier is selected from the group consisting of sucrose, dextrose, trehalose, mannitol, lactose, glycerol, and mixtures thereof.

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72. (New) The dispersion of claim ¹²56 that is isotonic with blood.

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73. (New) The dispersion of claim ¹²56 that is suitable for intravenous injection.

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74. (New) The dispersion of claim 56 that contains a pharmaceutically acceptable water-soluble polyhydroxy additive that provides an osmolality of about 250 to about 700 milliosmolal.

B²
cont.
75. (New) The dispersion of claim 74, wherein the osmolality is about 300 to about 500 milliosmolal.

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76. (New) The dispersion of claim 56, that has a viscosity from about 2 to about 5 centipoise.